PATENT
Attorney Docket No. 401301/A.BRAUN

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

HUBER et al.

Application No. Unassigned

Filed: July 26, 2001

For: PHARMACEUTICAL COMPOSITIONS

Art Unit: Unassigned

Examiner: Unassigned

AMENDMENTS TO SPECIFICATION AND CLAIMS MADE VIA PRELIMINARY AMENDMENT

Amendment to the paragraph beginning at page 6, line 1 :

WO-A-97/23199 attempted on the other hand to achieve advantageous release characteristics for 5-aminosalicylic acid by choosing certain excipients in combination ~~[lacuna]~~ with an optimal geometric shape of granule particles, and to ensure the bioavailability thereof both in the small intestine and in the large intestine. The disclosed granule particles have a core containing 5-aminosalicylic acid and a so-called spheronizing agent, preferably microcrystalline cellulose, and a coating of a semipermeable polymer, preferably ethylcellulose. In addition, the granule particles are intended to be essentially spherical and have a so-called aspect ratio, which is defined as the ratio of the longest to the shortest dimension of the particles, of 1.00-1.25. No coating insoluble in gastric and intestinal juices is incorporated in the particle matrix itself, and the described particles are moreover not very mechanically stable.

Amendment to the paragraph beginning at page 10, line 8:

The release delaying in the composition of the invention takes place due to a combination of at least three measures, each of which contributes to delaying the release of active ingredient, namely by mixing the active ingredient with a polymer insoluble in gastric and intestinal juices (i.e. through formation of a particle matrix), through the small pore size, which is related to a corresponding compaction of the core material, and by coating with a polymer

insoluble in gastric and intestinal juices. This method has the advantage inter alia that the release delaying is substantially independent of the shape and size of the particles and that it is therefore also possible to use nonspherical particles or particles differing in size. It has moreover emerged that very efficient release delaying is possible in this way even with small amounts of insoluble polymer and therefore delayed release formulations with a very high content of up to about 97% by weight active ingredient are possible. In addition, the type of release delaying of the invention does not depend on a possible external phase (e.g. tablet excipients), and the release delaying of the particles is, in contrast to previously disclosed formulations, not significantly impaired by compression to tablets either, because the highly compacted, lacquered matrix particles used according to the invention are very mechanically stable. The type of release delaying of the invention moreover has the advantage that perfectly divisible pharmaceutical forms, for example divisible delayed-release tablets (e.g. with score) are possible because the release delaying is unaffected by the division. It has additionally been found ~~[lacuna]~~ that the compositions of the invention are less affected by aging and temperature variations and therefore no significant changes in the release properties are to be observed even after prolonged storage.

Amendment to the title of the claims:

~~Patent Claims~~ WHAT IS CLAIMED IS:

Amendments to existing claims:

3. (Amended) A composition as claimed in claim 1~~or 2~~, wherein the polymer present in the core of the coated active ingredient-containing particles and/or the polymer present in the coating of the coated active ingredient-containing particles is a polymer which is able to swell and/or be eroded in gastric and/or intestinal juices.

4. (Amended) A composition as claimed in ~~any of claims~~ claim 1~~to 3~~, wherein the polymer present in the core of the coated active ingredient-containing particles and/or the polymer present in the coating of the coated active ingredient-containing particles is a cellulose ether, a cellulose ester or a polymer or copolymer of acrylic and/or methacrylic esters~~, preferably a copolymer of acrylic and methacrylic esters~~.

5. (Amended) A composition as claimed in ~~any of claims~~ <u>claim</u> 1 ~~to 4~~, wherein the core of the coated active ingredient-containing particles contains 2-30% by weight of polymer insoluble in gastric and intestinal juices, based on the active ingredient, and/or the coating of the coated active ingredient-containing particles contains 2-30% by weight of polymer insoluble in gastric and intestinal juices, based on the active ingredient.

6. (Amended) A composition as claimed in ~~any of claims~~ <u>claim</u> 1 ~~to 5~~, wherein the coated active ingredient-containing particles have a particle size of from 0.1 to 3.0 mm~~, preferably 0.2 to 2.5 mm~~.

7. (Amended) A composition as claimed in ~~any of claims~~ <u>claim</u> 1 ~~to 6~~, wherein the majority of the coated particles have a sphericity according to Wadell of less than 0.9.

8. (Amended) A composition as claimed in ~~any of claims~~ <u>claim</u> 1 ~~to 7~~, wherein the active pharmaceutical ingredient is an active ingredient from the group of antidiabetics, analgesics, antiinflammatory agents, antirheumatic agents, antihypotensives, antihypertensives, psychopharmaceuticals, tranquilizers, antiemetics, muscle relaxants, glucocorticoids, agents for treating ulcerative colitis or Crohn's disease, antiallergics, antibiotics, antiepileptics, anticoagulants, antimycotics, antitussives, arteriosclerosis remedies, diuretics, enzymes, enzyme inhibitors, gout remedies, hormones and their inhibitors, cardiac glycosides, immunotherapeutics and cytokines, laxatives, lipid-lowering agents, migraine remedies, mineral preparations, otologicals, antiparkinson agents, thyroid therapeutics, spasmolytics, platelet aggregation inhibitors, vitamins, cytostatics and metastasis inhibitors, phytopharmaceuticals, chemotherapeutics and amino acids.

9. (Amended) A composition as claimed in ~~any of claims~~ <u>claim</u> 1 ~~to 8~~, wherein the active pharmaceutical ingredient is an active ingredient from the group of analgesics, agents for treating ulcerative colitis or Crohn's disease, corticosteroids, proton pump inhibitors, virus statics, lipid-lowering agents, H2 blockers, antibiotics and ACE inhibitors.

10. (Amended) A composition as claimed in ~~any of claims~~ <u>claim</u> 1 ~~to 9~~, wherein the active pharmaceutical ingredient is tramadol, morphine, 5-aminosalicylic acid, budesonide, omeprazole, acyclovir, simvastatin, pravastatin, ranitidine, famotidine, amoxicillin,

clavulanic acid, enalapril, amlodipine or a pharmaceutically acceptable salt or derivative thereof.

11. (Amended) A composition as claimed in ~~any of claims~~ claim 1 ~~to 10~~, in the form of tablets, sugar-coated tablets, capsules, film-coated tablets, disperse tablets, lingual disperse tablets, effervescent tablets, sachets, powders for reconstitution or suppositories.

12. (Amended) A composition as claimed in ~~any of claims~~ claim 1 ~~to 11~~, in the form of tablets containing microcrystalline cellulose, water-soluble polyvinylpyrrolidone and crosslinked water-insoluble polyvinylpyrrolidone as tablet excipients.

13. (Amended) A composition as claimed in ~~any of claims~~ claim 1 ~~to 12~~ in the form of a divisible delayed release tablet.

14. (Amended) A process for producing a pharmaceutical composition as claimed in ~~any of claims~~ claim 1 ~~and 3 to 13~~, which comprises the active pharmaceutical ingredient being mixed with a polymer insoluble in gastric and intestinal juices and compacted to a composition in such a way that the compacted composition has an average internal pore diameter, measured by mercury porosimetry at 1000 to 4000 bar, not exceeding 35 µm, and comprises the compacted composition being comminuted to particles, and the particles being coated with a polymer insoluble in gastric and intestinal juices, and comprises, ~~if required~~ optionally, the coated particles being converted into a suitable dosage form.

15. (Amended) A process for producing a pharmaceutical composition as claimed in ~~any of claims~~ claim 2 ~~to 13~~, which comprises the active pharmaceutical ingredient being mixed with a polymer insoluble in gastric and intestinal juices and compacted to a composition in such a way that the compacted composition has a percent porosity not exceeding 27%, and comprises the compacted composition being comminuted to particles, and the particles being coated with a polymer insoluble in gastric and intestinal juices, and comprises, ~~if required~~ optionally, the coated particles being converted into a suitable dosage form.

16. (Amended) A process as claimed in claim 14 ~~or 15~~, wherein for mixing the active pharmaceutical ingredient with the polymer insoluble in gastric and intestinal juices the

active ingredient is moistened with an aqueous and/or organic dispersion or solution of the polymer, and the mixture is granulated and dried.

~~16.~~ 17. (Amended) A process as claimed in ~~any of claims~~ claim 14 ~~to 16~~, wherein the compaction takes places under a pressure of at least 5 kN per cm length of press.